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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KOLKER, DANIEL E	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 10/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/701,263	AKIL ET AL.	
	Examiner	Art Unit	
	Daniel Kolker	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The remarks, sequence listing, and amendments filed 18 August 2006 have been entered. Claims 2 – 29 are canceled; claim 30 is new. Claims 1 and 30 are pending and under examination.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Rejections and Objections

3. The following rejections and objections set forth in the previous office action are withdrawn:

A. Any rejection or objection of a canceled claim is now moot.

B. The objection to the claims is withdrawn in light of the amendment.

C. The rejection under 35 USC 112, first paragraph for lack of adequate written description is withdrawn in light of the amendment.

Rejections Maintained

Claim Rejections - 35 USC § 112

4. Claims 1 and 30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for detecting expression of human FGFR2 receptor nucleic acid in the dorsolateral prefrontal cortex of a deceased patient and concluding that the patient had major depression disorder, does not reasonably provide enablement for determining if the patient is predisposed to depression. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and used the invention commensurate in scope with these claims.

This rejection is maintained for the reasons of record and explained in further detail herein. Note that several aspects of the rejection have been withdrawn due to applicant's amendment, as the claims are now limited to a specific brain region and a specific mood disorder. Briefly, the specification discloses results obtained from post-mortem human brain samples. The results indicate that those patients who had a certain form of depression showed decreased FGFR2 mRNA in a certain brain region as compared to those patients who did not have depression. Independent claim 1 is drawn to "[a] method for determining whether a subject is predisposed for" this form of depression (emphasis added). The claim is not drawn to

whether or not a patient has the disorder, or had the disorder when living, or may have been more likely than not to develop the disorder had the patient continued to live. In fact, applicant has canceled language encompassing whether the patient has the depression disorder; all that is left is determining whether or not the patient is predisposed to develop the disorder.

Applicant has defined the usage of "predisposed" within the specification, at paragraph [82] on p. 20. The definition is reproduced below:

> [82] One who is "predisposed for a mental disorder" as used herein means a person who has an inclination or a higher likelihood of developing a mental disorder when compared to an average person in the general population.

Applicant argues, on p. 7 of the remarks filed 18 August 2006, that "the claimed method is useful for determining... whether a deceased subject might have suffered from a major depression disorder". The examiner concedes that this is a specific and substantial use of the claimed invention, however the question is not whether or not the method is useful for anything but whether it achieves the goal set forth in the preamble. The goal is not determining whether a deceased subject suffered from a major depression disorder, but rather is a method of determining whether a patient "has an inclination or a higher likelihood of developing a mental disorder when compared to an average person in the general population" according to applicant's own definition (here, of course, the mental disorder is limited to major depression disorder). The only data relating expression of SEQ ID NO:1 to major depression disorder were obtained from dead patients. The post-filing publication by Evans et al. (PNAS 101:15506-15511, of record), which is authored by all the inventors amongst others and appears to be drawn to the same data, specifically states that the data do

> not address whether the observed dysregulation represents a predisposing factor to the illness or a consequence of the disease process. Determining the exact role of the FGF system in mood disorders would require genomic analysis to ascertain the presence of allelic variations in genes that might vulnerability genes for severe depression. The present findings suggest that FGF family members, especially... FGFR2... are candidates genes for such a genomic analysis. (Evans, p. 15510, final complete paragraph)

Clearly, even a year after the filing of the non-provisional application and two years after the filing of the provisional applications, the inventors considered that considerably more work

must be done in order to determine if the changes in gene expression in fact represent a predisposition to the disease.

There are many factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (FED. Cir. 1988).

Here, the nature of the invention is complex. There are no working examples of prediction of whether or not patients get major depression disorder. There are no working examples of determining whether one is predisposed, as claimed, to the disorder. The only examples in the specification use post-mortem tissue, which cannot be used to determine if the patient will develop a disease in the future as the patients in fact have no future. A year after the instant application was filed, the inventors wrote that it was unclear whether the changes in gene expression reflected a predisposition to disease or alternatively were a consequence of the disease process itself. At that time, the inventors set forth the experimentation that would need to be performed in order to resolve the issue. Given the lack of guidance in the specification as filed, the degree of experimentation required, the lack of working examples of determining whether one is predisposed to the disorder, and the complex nature of the invention, it would require undue experimentation to make and use the invention commensurate in scope with the claims. The specification must form an enabling disclosure at the time of filing; see MPEP § 2164.05(a) and *In re Hogan and Banks* (194 USPQ 527), where the court emphasized that a patent specification must teach how to make and use the invention at the time of filing. In the instant situation, the specification is not enabling for determining if a patient is predisposed to the disorder. This is evidenced by the post-filing reference by Evans.

On p. 7 of the remarks, applicant states that the examiner ignores the fact that skilled artisans recognize that post-mortem data are relevant to pre-deceased subjects. The examiner is quite aware that the data are generally reflective of the pre-deceased state of nucleic acid expression. This assertion is corroborated by the scientific articles by Bahn et al. and Franz et al., submitted by applicant with the remarks. However, what is not enabled by the specification or the prior art is using such samples from diseased patients to determine whether or not the

changes observed with disease are predictors of whether or not an unaffected patient will develop disease in the future. Applicant also argues (p. 9 of the remarks) that a rigorous or invariable correlation need not be established, that a reasonable correlation will suffice for the purposes of enablement. Here, however, there is a reasonable correlation between gene expression post-mortem and pre-mortem, but there is no correlation presented between post-mortem samples from diseased patients and prediction that an unaffected patient will have a disease in the future. Thus the citation of *Cross v Iizuka* is not germane to the instant discussion.

5. Claims 1 and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

This rejection is maintained for the reasons of record with respect to claim 1. It now applies to claim 30, the newly-added dependent claim. To the extent that the previous rejection covered use of the term "stringent conditions" the rejection is now moot, as that language has been canceled from claim 1. The term "selectively associates" in claim 1 is a relative term which renders the claim indefinite. The term "selectively associates" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Applicant argues that "selectively associates" is not indefinite but provides no evidence as to the precise definition of "selectively". It is unclear from the specification and the claims whether this term means that the nucleic acids should associate with a weak affinity or a strong affinity, for example. The term might mean that the two nucleic acids are to hybridize to each other and to no other nucleic acids. Or it could mean that the two nucleic acids briefly "associate" with one another during the dynamic process of hybridization, only to be dissociated later. Use of the term "selectively" in the absence of a modifier such as "weakly" is indefinite as it unclear what the required degree of selectivity is.

It is recommended that to overcome the rejection applicant consider amending claim 1 to delete the "selectively associates" language and that the claim recite that the probe or "nucleic acid reagent" to be used have a requisite degree of identity with SEQ ID NO:1. As it stands, there is no requirement that the "nucleic acid reagent" have any particular structure, only that it "selectively associate" with a nucleic acid at least 95% identical to SEQ ID NO:1.

Double Patenting

6. Claims 1, 3 – 4, and 6 – 10 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3 – 4, and 6 – 10 of copending Application No. 11/158530. Although the conflicting claims are not identical, they are not patentably distinct from each other because they appear to be identical with the exception of the numbers of the tables to which claim 1 refers in each case. The specification of the '530 application clearly encompasses detection of FGFR2 nucleic acid with a microarray (see p. 67 paragraph 294). Thus the claims in the '530 application read in light of the specification would render obvious the pending claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant did not traverse this rejection.

Rejections Necessitated by Amendment

Claim Rejections - 35 USC § 112

7. Claims 1 and 30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 1 has been amended. It now allows for use of nucleic acid reagents which bind to sequences at least 95% identical to SEQ ID NO:1. The examiner can find support for SEQ ID NO:1, for hybridization assays wherein SEQ ID NO:1 is detected, and contemplation of mutants at least 95% identical to SEQ ID NO:1. However, the examiner cannot find support for using a nucleic acid reagent which binds to sequences which are variants of SEQ ID NO:1. There is no support for detecting variants of the disclosed sequences, as opposed to the sequences themselves, in the specification and claims as originally filed. Note that following the suggestion set forth at the end of paragraph number 5 may also obviate this rejection.

8. Claims 1 and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "significantly less than the control" in claim 1 part (iv) is a relative term which renders the claim indefinite. The term "significantly less than the control" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is unclear when a difference between a control and experimental sample might be considered significant. It could be a 1% change, a 10% change, or a 50% change. It is not clear whether the artisan is to determine significance in his or her own mind or alternatively whether a statistically significant difference must be present.

Claim 30 is limited to deceased subjects but as it depends from claim 1 it requires determining if a subject is predisposed to acquiring a disorder. A dead person cannot be predisposed to any disease or condition, as the person is already dead. The claim is confusing as it is unclear how a skilled artisan would be able to determine that a person who cannot get any more diseases will be more likely to get diseases in the future.

Conclusion

9. No claim is allowed.

10. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. El-Husseini et al. 1994. Molecular and Cellular Endocrinology 104:191-200. The reference teaches detection of mRNA encoding FGFR2 in the brains of deceased animals and the authors do not conclude that the animals have depression. However the reference does not teach or suggest assaying dorsolateral prefrontal cortex.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel Kolker whose telephone number is (571) 272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

DK

Daniel E. Kolker, Ph.D.
October 12, 2006

ROBERT C. HAYES, PH.D.
PRIMARY EXAMINER